Phase I Pharmacokinetic Study of S-1 Granules and Nedaplatin for Advanced Head and Neck Cancer

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Abstract. *Aim: We performed a pharmacokinetic phase I trial of the combination of S-1 granules and nedaplatin for head and neck squamous cell carcinoma (HNSCC). Patients and Methods: Patients were treated with both nedaplatin on day 1 at a dose starting at 80 mg/m^2 (level 1) escalating up to 90 mg/m^2 (level 2), and S-1 granules at a daily dose of 80 mg/m^2 on days 1 to 14 every three weeks. The primary end-point was determination of the recommended dose. Results: Twenty patients were enrolled. Dose-limiting toxicities occurred in one out of six patients at dose level 1 (neutropenia) and in all three patients at level 2 (neutropenia and thrombocytopenia). The recommended dose was determined as level 1. Pharmacokinetic parameters of S-1 granule did not differ from the capsula formulation. The response rate was 42.1%. Conclusion: This combination was well-tolerated and manifested a promising activity against HNSCC.*

Squamous cell carcinoma of the head and neck (HNSCC) accounts for ~4% of all cancers worldwide (1). Most individuals with recurrent or metastatic HNSCC have a poor prognosis that has remained largely unchanged over the past 30 years. Although the combination of cisplatin and fluorouracil has been the mainstay of first-line treatment for patients with advanced HNSCC, the median survival time for such treated individuals is typically only ~10 months (2, 3). Furthermore, the need for continuous infusion of fluorouracil together with a large volume of physiological saline to minimize the nephrotoxicity of cisplatin constitutes a severe burden for patients with HNSCC. The development of alternative treatment regimens that are both convenient and safe for such patients is thus urgently required.

Nedaplatin, which was developed as an analog of cisplatin, has shown an efficacy equivalent to that of cisplatin in terms of response rate in patients with HNSCC (4, 5). As a result of its lower nephrotoxicity, however, this platinum agent does not require the high volume of hydration necessary for cisplatin. S-1 was developed as an oral fluoropyrimidine capsule formulation that consists of tegafur [a pro-drug of 5-fluorouracil (5-FU)], 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate at a molar ratio of 1:0.4:1 (6). Over the past decade, S-1-based chemotherapy has been recognized as a standard treatment for individuals with advanced gastric cancer or non–small cell lung cancer (7, 8). Furthermore, a phase II trial of the capsular formulation of S-1 (S-1 capsule) administered as a single-agent revealed a response rate of 28.8% and a feasible toxicity profile in patients with recurrent HNSCC (9). However, many patients with HNSCC have difficulty in swallowing medication in capsular form, especially after surgery or radiotherapy. A granular formulation of S-1 (S-1 granule) has, therefore, recently been developed for such individuals. S-1 granule can be administered orally or *via* a gastrostomy tube in patients with dysphagia. However, little is known regarding the safety and pharmacokinetic profile of S-1 granule-based chemotherapy.

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In the present study we investigated the safety and efficacy of the combination of S-1 granules and nedaplatin for patients with recurrent or metastatic HNSCC. We also assessed the pharmacokinetic profiles of nedaplatin as well as of S-1 components and 5-FU after dosing with the S-1 granular formulation. As far as we are aware of, the present study is the first phase I dose-finding and pharmacokinetic trial for S-1 granules.

Patients and Methods

Patient eligibility. Eligible patients were 20 years of age or older with a confirmed diagnosis of HNSCC (with the exception of thyroid cancer). They were required to have an Eastern Cooperative Oncology Group performance status of <2 and adequate organ function. Previous treatments, including chemotherapy, radiotherapy, and surgery, were allowed if they had been completed at least four weeks before registration. Previous administration of neither nedaplatin nor S-1 was permitted, however. Patients with other serious illnesses or medical conditions such as uncontrolled infection, other malignancies, or central nervous system metastases that were still symptomatic were also not eligible for participation. All participants received information about the nature and purpose of the study, and they provided written informed consent in accordance with institutional guidelines.

Study design and patient selection. The study was designed as a single-center, open-label, dose-escalation phase I trial. The primary objectives were to determine the recommended dose (RD) for the combination of S-1 granules and nedaplatin, as well as to collect overall safety data. Secondary objectives included determination of the maximum tolerated dose (MTD) and pharmacokinetic variables, as well as preliminary assessment of antitumor activity in the treatment population. The study was reviewed and approved by the Institutional Review Board of Kinki University, Faculty of Medicine (approval no. 2010231).

Treatment schedule. Patients received a fixed daily dose of S-1 granules (40 mg/m^2, twice daily) for 14 consecutive days (days 1 to 14) and a 90-min intravenous infusion of nedaplatin on day 1 every 21 days until disease progression or development of intolerable toxicity. Patients unable to swallow S-1 granules were allowed to dissolve them in water. The dose of nedaplatin was set at 70 mg/m^2 (level 0), 80 mg/m^2 (level 1 as the starting dose), 90 mg/m^2 (level 2), or 100 mg/m^2 (level 3), with the dose escalation following a traditional 3+3 phase I trial design. The escalation-reduction scheme for nedaplatin dose was based on the occurrence of a drug-related dose-limiting toxicity (DLT) within the first treatment cycle. A DLT was defined as a toxicity occurring in cycle 1 that met one of the following criteria: neutropenia of grade 4 persisting for 4 days or more, febrile neutropenia, thrombocytopenia of grade 4, a serum creatinine level of 2.0 mg/dL or more, or a non-hematological toxicity (with the exception of nausea, vomiting, or anorexia) of grade 3 or 4. A delay of more than two weeks in administration of the second treatment cycle as a result of toxicity was also considered a DLT. If 67% or more of patients had a DLT at the same dose level, the dose was determined to be the MTD. The dose level immediately below the MTD was then defined as the RD. After determination of the RD, the corresponding cohort was to be expanded to an overall maximum of 20 patients for the study to allow a more complete assessment of the safety and tolerability of the dose level. At least 14 patients were to be treated at the RD, and the probability of adverse events (AEs) with an incidence of 20% or more not being detected in any of the 14 patients was 4.4%.

If a DLT was not observed in any of the initial three patients in the first cohort (level 1), an escalated dose of nedaplatin (90 mg/m^2) was to be administered to a second cohort of three patients at level 2. If a DLT was observed in one or two out of the first three patients, however, an additional three patients were to be enrolled to assess the tolerability to this dose level. If a DLT occurred in no more than two of the six patients at level 1, the dose of nedaplatin was then to be increased (to 90 mg/m^2). If three or more of the six patients at level 1 experienced a DLT, additional patients were to be recruited at level 0. In addition to this dose escalation-reduction scheme, if the investigators and an independent data-monitoring committee agreed that additional patients were necessary to confirm the dose escalation-reduction decision in cases in which three or more patients experienced DLTs that were not life-threatening and were reversible and manageable, then the entry of additional patients at that dose level was to be allowed.

Patient evaluation. The safety and tolerability of the combination of S-1 granules and nedaplatin were assessed according to Common Toxicity Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/c

Table I. *Characteristics of the study patients (n=20), the median age of whom was 63 years (range: 53-73 years).*

Characteristics	No. of patients
Gender	
Male	15 (75%)
Female	5 (25%)
Performance status (ECOG)	
0	7 (35%)
1	13 (65%)
Primary tumor site	
Hypopharynx	6 (30%)
Oral (including tongue and hard palate)	5 (25%)
Nasopharynx	5 (25%)
Oropharynx	3 (15%)
Larynx	1 (5%)
Previous treatment	
Surgery	1 (5%)
Surgery and radiation	12 (60%)
Surgery and chemoradiotherapy	2 (10%)
Chemoradiotherapy	5 (25%)
Site of metastasis	
Local	6 (30%)
Lung	7 (35%)
Liver	3 (15%)
Bone	3 (15%)
Lymph nodes	5 (25%)
Smoking history	
Never	7 (35%)
Current or former	13 (65%)

ECOG, Eastern Cooperative Oncology Group.

Table II. *Dose-escalation scheme and dose-limiting toxicities (DLTs).*

Dose level	Nedaplatin (mg/m^2)	S-1 granules (mg/m^2)	No. of patients		Type of DLT
			Total	DLT in first course	
1	80	80	6	1	Delay of second treatment cycle[a]
2	90	80	3	3	Delay of second treatment cycle[a] or thrombocytopenia

[a]Due to neutropenia.

tcaev3.pdf). Radiological tumor assessment was performed every 2 months to confirm response until progression. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (10). Progression-free survival (PFS) was calculated as the time from the first day of treatment to the first day of documented progression or death. Overall survival (OS) was calculated from the first day of the combination therapy until death from any cause or the date of last contact. The probability of survival as a function of time was estimated with the Kaplan Meier method. Analyses were performed with SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA).

Pharmacokinetics. The plasma pharmacokinetics of single-agent and combination treatments were investigated in the dose-escalation phase of the study in order to assess the fate of S-1 granules and the potential for interaction between nedaplatin and S-1 at each dose level. The pharmacokinetics of both S-1 and nedaplatin were evaluated on day 1 immediately before and 1, 2, 4, 8, and 24 h after administration of nedaplatin during cycle 1, in which S-1 was administered simultaneously with nedaplatin. The pharmacokinetics of S-1 monotherapy were evaluated on day 1 immediately before and 1, 2, 4, and 8 h after S-1 administration during cycle 2, in which nedaplatin was administered on day 2 for the purpose of this evaluation.

The plasma concentration of nedaplatin was measured by NAC Co. Ltd. (Tokyo, Japan). The plasma concentrations of S-1 components (tegafur, CDHP, and potassium oxonate) and 5-FU were measured by FALCO Biosystems (Kyoto, Japan). All concentrations were determined with the use of liquid chromatography and tandem mass spectrometry (11). Differences in pharmacokinetic parameters were evaluated with Student's *t*-test, and a *p*-value of <0.05 was considered statistically significant.

Results

Patients' characteristics. The characteristics of the 20 study patients are summarized in Table I. The median age was 63 years, with a range of 53 to 73 years. All patients had recurrent cancer, having previously undergone definitive radiotherapy or surgery for their primary sites. Six individuals had locally recurrent disease, whereas 14 patients had metastases.

Dose escalation and determination of MTD and RD. Given that one out of the first three patients at dose level 1 experienced a DLT, a delay of more than two weeks occured in administration of the second treatment cycle because of neutropenia development, an additional three patients were treated at this dose level (Table II). None of these three additional patients experienced a DLT, and so three patients were then entered at dose level 2. All three patients at dose level 2 experienced a DLT; thrombocytopenia of grade 4 in one patient; delay of more than two weeks in the second treatment cycle due to the development of neutropenia in two patients) in the first cycle, with dose level 2 thus being identified as the MTD. According to the protocol definition, dose level 1 was determined to be the RD, and an additional 11 patients were assigned to this level. A total of 17 patients were, therefore, treated at dose level 1.

Treatment administered. A total of 142 cycles of chemotherapy were administered, with a median of six treatment cycles per patient (range: 2-21). The mean relative dose intensities of S-1 and nedaplatin were 88.4% and 95.9%, respectively. Dose reductions were uncommon, being necessary according to the study protocol in only 10 cycles (7.0% of total cycles) because of neutropenia in six patients, thrombocytopenia in three patients, and febrile neutropenia in one patient. A dose delay occurred in 19 cycles (13.4% of total cycles), in most cases as a result of insufficient bone marrow function.

Safety. The major AEs during the entire treatment period are shown in Table III. The most frequent AEs were leukopenia, neutropenia, thrombocytopenia, fatigue, and anorexia, all of which were clinically manageable. The most common toxicities of grade 3 or 4 were leukopenia (24% at dose level 1), neutropenia (29%), and thrombocytopenia (29%). Non-hematological AEs of grade 3 or 4 were not apparent, with the exception of grade 3 rash in one patient and grade 3 febrile neutropenia in another, and there were no treatment-related deaths. The most frequent reason for discontinuation of therapy was disease progression (n=13, 65%), followed by the occurrence of AEs (n =5, 25%).

Pharmacokinetics. Eight patients (five at dose level 1 and three at dose level 2) in the dose-escalation phase of the study were evaluable for pharmacokinetic analysis. The plasma concentrations of S-1 components and 5-FU on day 1 of both the first and second treatment cycles are shown in

Table III. *Treatment-related adverse events according to treatment cohort and grade.*

	Dose level 1 (n=17)			Dose level 2 (n=3)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Hematological						
Anemia	4 (24)	0	0	1 (33)	0	0
Thrombocytopenia	10 (59)	4 (24)	1 (6)	3 (100)	1 (33)	1 (33)
Leukopenia	11 (65)	4 (24)	0	3 (100)	1 (33)	1 (33)
Neutropenia	10 (59)	2 (12)	3 (18)	3 (100)	2 (67)	1 (33)
Nonhematological						
Fatigue	10 (59)	0	0	2 (67)	0	0
Anorexia	9 (53)	0	0	0	0	0
Nausea	6 (35)	0	0	1 (33)	0	0
Rash	4 (24)	1 (6)	0	2 (67)	0	0
Stomatitis	4 (24)	0	0	1 (33)	0	0
Diarrhea	3 (18)	0	0	1 (33)	0	0
Constipation	3 (18)	0	0	0	0	0
Vomiting	2 (12)	0	0	0	0	0
AST increase	1 (6)	0	0	0	0	0
ALT increase	1 (6)	0	0	0	0	0
Hyperbilirubinemia	1 (6)	0	0	1 (33)	0	0
Febrile neutropenia	1 (6)	1 (6)	0	1 (33)	0	0

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

Figure 1. The mean values for the area under the plasma concentration *versus* time curve over 8 h (AUC_{0-8}) and for the maximal concentration (C_{max}) of 5-FU, tegafur, and CDHP did not differ significantly between S-1 granule administration with (cycle 1) or without (cycle 2) nedaplatin, whereas the AUC_{0-8} and C_{max} of potassium oxonate were significantly greater for S-1 administration together with nedaplatin (Table IV). Pharmacokinetic analysis was also performed for the plasma concentration of nedaplatin on day 1 of combination therapy with nedaplatin and S-1 granules (Table V). The increase in the mean value of AUC_{0-24} for the total platinum at dose level 2 compared with the dose at level 1 was consistent with the increase in nedaplatin dose.

Efficacy. Nineteen out of the 20 patients were evaluable for antitumor response, with the remaining patient treated at dose level 2 not being available for such assessment. One patient showed a complete response and seven patients showed a partial response, yielding an overall response rate of 42.1% [95% confidence interval (CI): 19.3-64.9%]. Four patients had stable disease, giving an overall disease control rate of 63.2% (95% CI: 40.9-85.5%). Out of the five patients with nasopharyngeal cancer, four achieved a partial response. The median PFS and OS for all 20 treated patients were 5.5 months (95% CI: 2.2-8.7 months) and 12.0 months (95% CI: 6.5-17.6 months), respectively.

Discussion

S-1, which is a new oral fluorinated pyrimidine formulation was designed to enhance the efficacy of 5-FU by maintaining therapeutic plasma 5-FU concentrations at a therapeutic level for a long time, and to reduce the gastrointestinal toxicity of tegafur. Patients with HNSCC often experience a deterioration in swallowing function, especially after radiation therapy or surgery (12, 13). Such patients thus have difficulty swallowing medication in capsular form. Given that the granules formulation of S-1 can be administered as a liquid preparation, even HNSCC patients with dysphagia can now easily take this drug. In the present study, three patients who had been previously treated with both radiotherapy and surgery for their primary tumors were able to receive S-1 granules *via* a gastrostomy tube. However, whereas the safety and pharmacokinetics of S-1 capsules have been characterized substantially, such profiles for the new granulear formulation have remained largely unknown. We have now found that the pharmacokinetic parameters for S-1 granules do not appear to substantially differ from those previously determined for S-1 capsules (14), suggesting that neither the absorption nor metabolism of the components of S-1 differs between the two formulations.

Nedaplatin has been recognized as being potentially active for SCC, with its administration being more convenient than that of

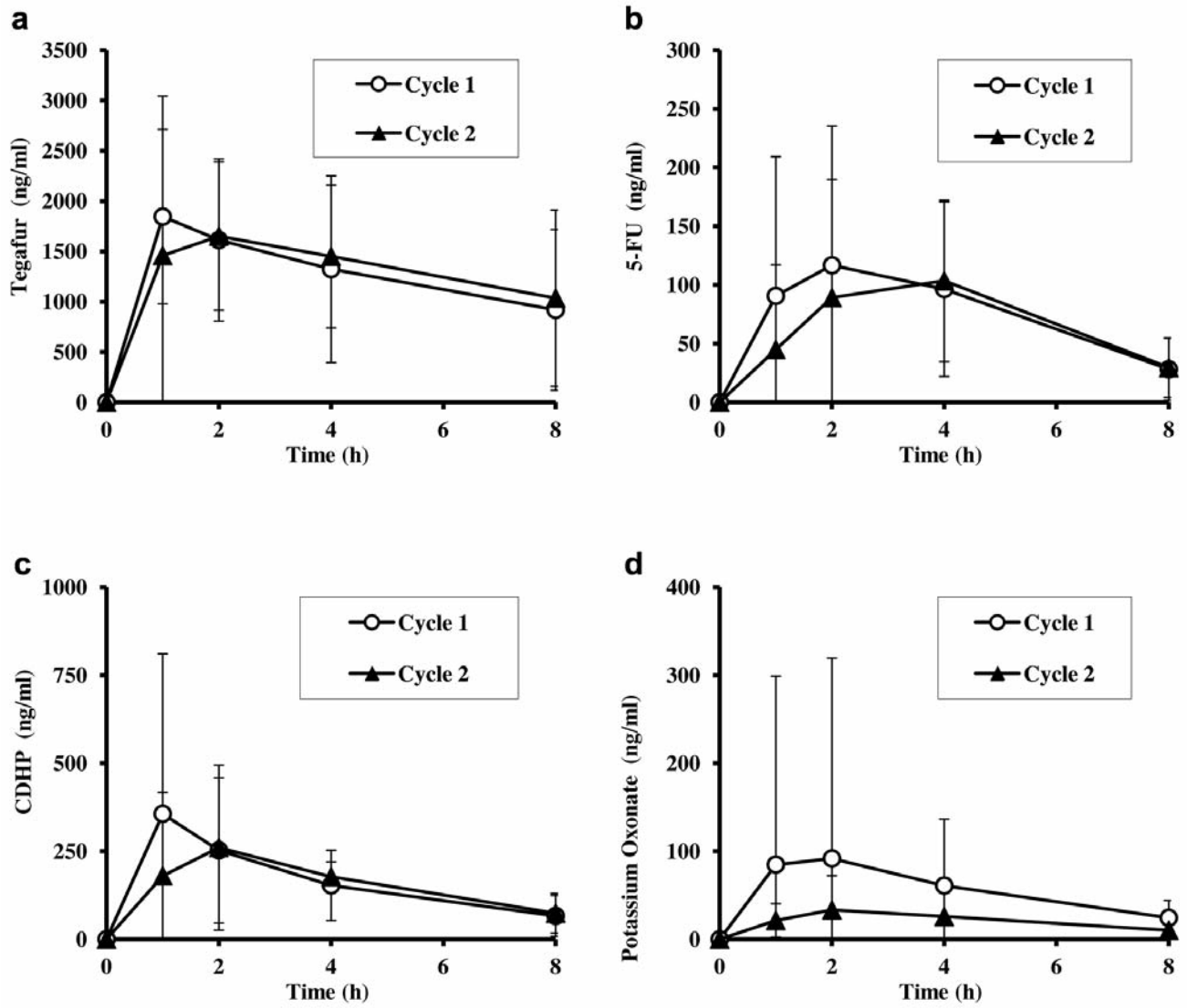

Figure 1. *Plasma concentration versus time curves for S-1 components and 5-FU after administration of S-1 granules (40 mg/m2, twice daily) either in combination with nedaplatin (cycle 1) or as monotherapy (cycle 2). Data are means±SEM (n=8 patients) for tegafur (a), 5-FU (b), CDHP (c), and potassium oxonate (d).*

Table IV. *Pharmacokinetic parameters for S-1 components and 5-FU.*

	Cycle 1				Cycle 2			
Parameter	Tegafur	5-FU	CDHP	Oxonate	Tegafur	5-FU	CDHP	Oxonate
C_{max} (ng/ml)	1900.0±363.0	129.4±54.7	377.4±170.0	101.4±87.9	1896.0±443.0	105.9±38.0	274.5±78.2	34.6±19.1*
T_{max} (h)	1.6±1.0	2.7±1.0	1.6±1.0	3.1±2.2	1.9±1.4	3.5±0.9	2.3±0.7	2.0±0.9
$t_{1/2}$ (h)	6.7±2.0	2.4±0.9	3.1±0.8	3.0±0.9	8.9±6.4	1.56±0.34	3.1±0.9	2.9±0.6
AUC_{0-8} (ng/ml h)	9822.0±2350.0	733.3±318.2	1330.6±505.5	447.9±313.7	10,713.0±2223	612.0±283.9	1225.4±349.2	160.3±101.7*

Data are means±SEM (n=8 patients). C_{max}, Maximal plasma concentration; T_{max}, time to achieve C_{max}; $t_{1/2}$, plasma half-life; AUC_{0-8}, area under the plasma S-1 concentration *versus* time curve for 0 to 8 h; 5-FU: 5-fluorouracil; CDHP: 5-chloro-2,4-dihydroxypyridine; Oxonate: potassium oxonate. *$p<0.05$ *versus* the corresponding value for cycle 1 (Student's *t*-test).

Table V. *Pharmacokinetic parameters for nedaplatin at the two dose levels.*

	Dose level 1 (80 mg/m^2, n=5)		Dose level 2 (90 mg/m^2, n=3)	
Parameter	Total platinum	Free platinum	Total platinum	Free platinum
C_{max} (μg/mL)	3.90±0.85	3.42±0.72	4.65±0.89	4.09±0.92
T_{max} (h)	1.40±0.55	1.4±0.55	1.67±0.58	1.67±0.58
$t_{1/2}$ (h)	26.52±33.51	4.45±1.91	11.76±2.92	4.17±0.01
AUC_{0-24} (μg h/mL)	30.29±11.31	15.67±3.66	37.71±2.39*	21.58±1.93

Data are means±SEM. *p=0.04 *versus* the corresponding value for dose level 1 (Student's *t*-test).

cisplatin. In phase II trials in patients with non-small cell lung cancer, nedaplatin gave a favorable response rate in patients with a SCC histology when administered both as a single-agent and in combination treatment (15, 16). We, therefore, investigated the potential activity of the combination of nedaplatin and S-1 granules in patients with recurrent or metastatic HNSCC in a phase I dose-finding and pharmacokinetic trial. We found that most toxicities were mild or moderate in extent. Non-hematological AEs of grade 4 were not observed, and all toxicities of grade 3 or 4 were reversible and manageable with supportive treatment and dose reduction or interruption. In comparison with previous studies of nedaplatin monotherapy (17, 18), the plasma concentration profile and pharmacokinetic parameters for nedaplatin did not appear to be affected by co-administration of S-1. Although pharmacokinetic parameters for 5-FU, tegafur, and CDHP did not differ substantially between S-1 granules administered with or without nedaplatin, the AUC_{0-8} and C_{max} for potassium oxonate were significantly greater when S-1 granules were administered in combination with nedaplatin. Given that food intake has been found to affect the pharmacokinetics of potassium oxonate but not those of 5-FU, tegafur, or CDHP (19), the observed increase in the AUC_{0-8} and C_{max} of potassium oxonate in cycle 1 was possibly due to an effect of the fasting.

Although we are unable to reach any firm conclusion regarding the efficacy of the treatment regimen because of the small size of our phase I trial, we found that combination of S-1 granule and nedaplatin have a promising activity in patients with HNSCC, with an overall response rate of 42.1%, median PFS of 5.5 months, and median OS of 12.0 months. Although there are also limitations to the comparison of results among different studies, the efficacy data in our trial compare favorably with those reported in a previous phase III study of cisplatin and fluorouracil in patients with HNSCC (3). It is possible that the relatively good prognosis of patients with nasopharyngeal cancer patients, who accounted for 25% of the enrolled subjects, contributed to the observed favorable outcomes. However, the overall response rate (4/14, 28.6%) for patients with other types of HNSCC was also promising.

In conclusion, we have shown for the first time that the pharmacokinetics and safety of S-1 granules are similar to those of the capsular formulation. The granular formulation of S-1, thus, has the potential to serve as an alternative option for patients unable or unwilling to swallow the standard capsular formulation, without compromising exposure to S-1. The combination of S-1 granules and nedaplatin was well-tolerated by patients with HNSCC, and the RD of this combination was determined to be 80 mg/m^2 for nedaplatin on day 1 and 80 mg/m^2 for S-1 granules on days 1 to 14 every three weeks. This novel combination was also found to be a potentially active regimen for patients with recurrent or metastatic HNSCC, warranting further evaluation of its efficacy.

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